REMARKS

Entry of the foregoing amendment is requested. Claims 13-24 will be pending. Claims 22-24 receive support at page 7, lines 25 - end of the specification. The recitation of modes of administration at page 7, lines 20 et seq, make clear that humans are an intended subject. The recitation of 12-22 carbon atoms of the alkyl ester chain receives support from the claims and examples, we well as from U.S. Patent No. 6,337,065, which is incorporated by reference at page 4, line 7, and thus is part of the specification.

The Examiner has set forth a prior art rejection based upon Scivoletto, plus the Jacobson '065 patent. The rejection is traversed.

Scivoletto describes methyl nicotinic alkyl ester, which is outside of the claims, and "derivatives." No definition of what "derivative" means is given. The only statement made refers to "nicotinamides, nicotinic acids, nicotinic esters," and "derivatives" thereof. No guidance is given as to which is preferred, nor as to how long chain lengths should be.

The Examiner has *de facto* admitted that interpretation of "derivative" without explanation is not feasible. In the first Office Action, the Examiner cited Warshaw and Bernstein. It was pointed out that "nicotinic acid esters containing 7-12 carbon atoms" did not encompass claimed subject matter. Nicotinic acid itself contains 6 carbons, so clearly Warshaw is describing "derivatives." Yet these "derivatives" clearly do not fall within what is claimed. The same is true regarding Bernstein which teaches nicotinamide, and was apparently regarded as a derivative by the Examiner. The claims do not encompass nicotinamide.

The fact is, one is hard pressed to find any suggestion within Scivoletto as to where to look for the so-named "derivatives."

It is submitted that, given Scivoletto's teaching and clear preference, for the methyl ester, one would look to smaller esters.

There are issues with respect to the administration of nicotinic acid alkyl esters where the ester is too short. U.S. Patent No. 6,464,992, a copy of which is appended hereto, discusses the problem of dilation, with niacin esters of a log P less than 6. The relevant passage is highlighted for the Examiner.

Nicotinic acid alkyl esters with a log P of 6 or greater begin with 11 alkyls. Please see U.S. Patent No. 6,337,065, which the Examiner has made of record. Hence, one of ordinary skill in the art, charged with knowledge thereof, would recognize the issue of vasodilatation, and the problems associated therewith. As the literature makes clear, the redness and flushing associated with vasodilatation leads to compliance issues.

This being the case, one of ordinary skill in the art would not regard Scivoletto as teaching anything beyond its limited teaches. Combination with Jacobson '065 is certainly contraindicated and the rejection should be withdrawn.

Regarding the double patenting rejection, the Examiner miscomprehends applicants' argument. The argument is that the Examiner's position is not consistent. If the '234 patent was found patentable over the same set of references made of record here, and the current application is subject to double patenting issues, then it cannot be obvious over the same prior art. Applicants contend that the Examiner may properly propound one position or the other, but not both.

Withdrawal of the rejections is believed proper and is urged.

* * *

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 50-0624, under Order No. NY-NIAD 216-US2-DIV (104047460 from which the undersigned is authorized to draw.

Dated: January 21, 2009

Respectfully submitted,

By _____

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Attachment: U.S. Patent No. 6,464,992

PTO/SB/97 (09-04)
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Application No. (if known): 10/825,405 Attorney Docket No.: NY-NIAD 216-US2-DIV

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Amendment in Response to Non-Final Office Action (6 pages)
Copy of U.S. Patent No. 6,464,992

US006464992B2

(12) **United States Patent**
Jacobson et al.

(10) **Patent No.: US 6,464,992 B2**
(45) **Date of Patent: Oct. 15, 2002**

(54) **TOPICAL MICRONUTRIENT DELIVERY SYSTEM AND USES THEREOF**

(75) Inventors: **Elaine L. Jacobson**, Tucson, AZ (US); **Myron K. Jacobson**, Tucson, AZ (US); **Jaber G. Qasem**, Tucson, AZ (US); **Hyuntae Kim**, Tucson, AZ (US); **Moonsun Kim**, Tucson, AZ (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/832,571**

(22) Filed: **Apr. 11, 2001**

(65) **Prior Publication Data**

US 2002/0037898 A1 Mar. 28, 2002

Related U.S. Application Data

(60) Provisional application No. 60/197,828, filed on Apr. 14, 2000.

(51) **Int. Cl.**[7] **A61K 7/44**; A61K 7/48; A61F 2/02; A61F 13/02; A61L 15/16

(52) **U.S. Cl.** **424/401**; 424/78.03; 424/423; 424/433; 424/436; 424/447; 424/449

(58) **Field of Search** 424/401, 449, 424/78.03, 433, 436, 447, 423

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,185,325 A * 2/1993 Brown et al. 514/23

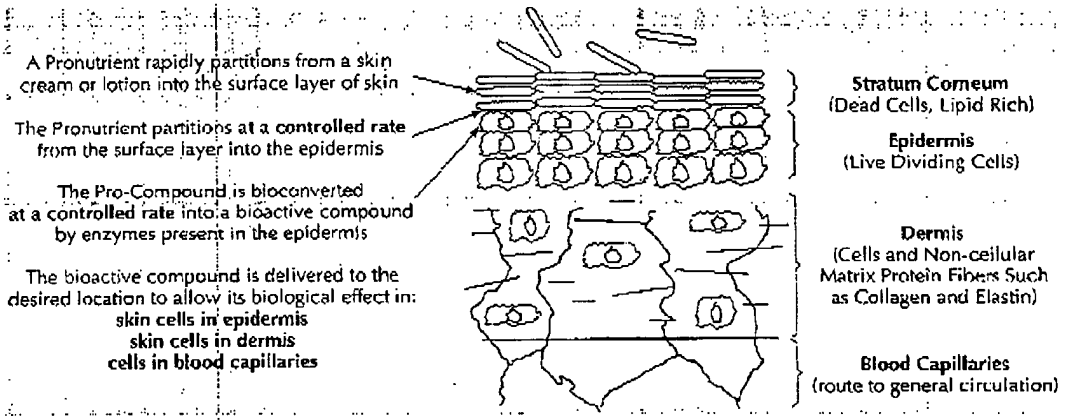
* cited by examiner

Primary Examiner—Carlos Azpuru
(74) *Attorney, Agent, or Firm*—Fulbright & Jaworski LLP

(57) **ABSTRACT**

The invention involves methods and compositions useful in delivering micronutrients to cells. By formulating the micronutrient in the form of an ester that is convertible to the active form of the micronutrient, one can combine it with a co-ester that inhibits esterases, so that the micronutrient can reach the targeted cells prior to degradation. Both methods and compositions are described.

48 Claims, 3 Drawing Sheets



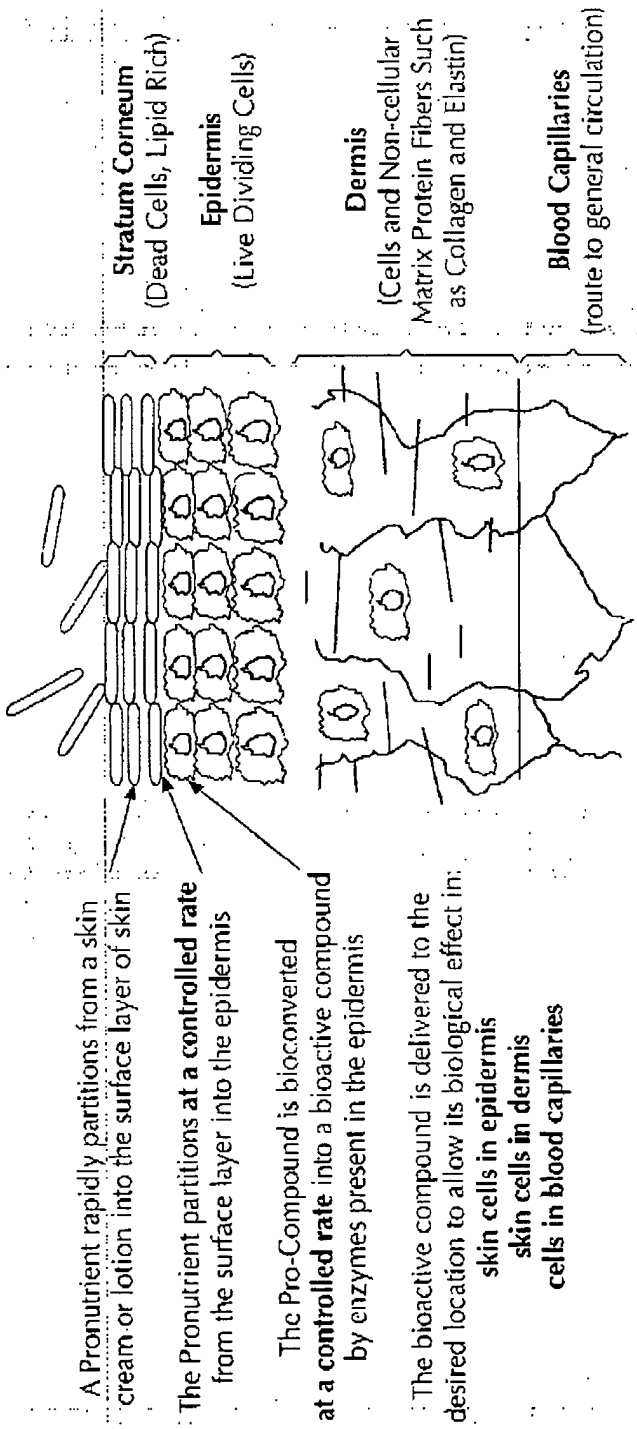

Stratum Corneum
(Dead Cells, Lipid Rich)
Epidermis
(Live Dividing Cells)
Dermis
(Cells and Non-cellular Matrix Protein Fibers Such as Collagen and Elastin)
Blood Capillaries
(route to general circulation)
A Pronutrient rapidly partitions from a skin cream or lotion into the surface layer of skin
The Pronutrient partitions at a controlled rate from the surface layer into the epidermis
The Pro-Compound is bioconverted at a controlled rate into a bioactive compound by enzymes present in the epidermis
The bioactive compound is delivered to the desired location to allow its biological effect in:
skin cells in epidermis
skin cells in dermis
cells in blood capillaries

FIG. 1

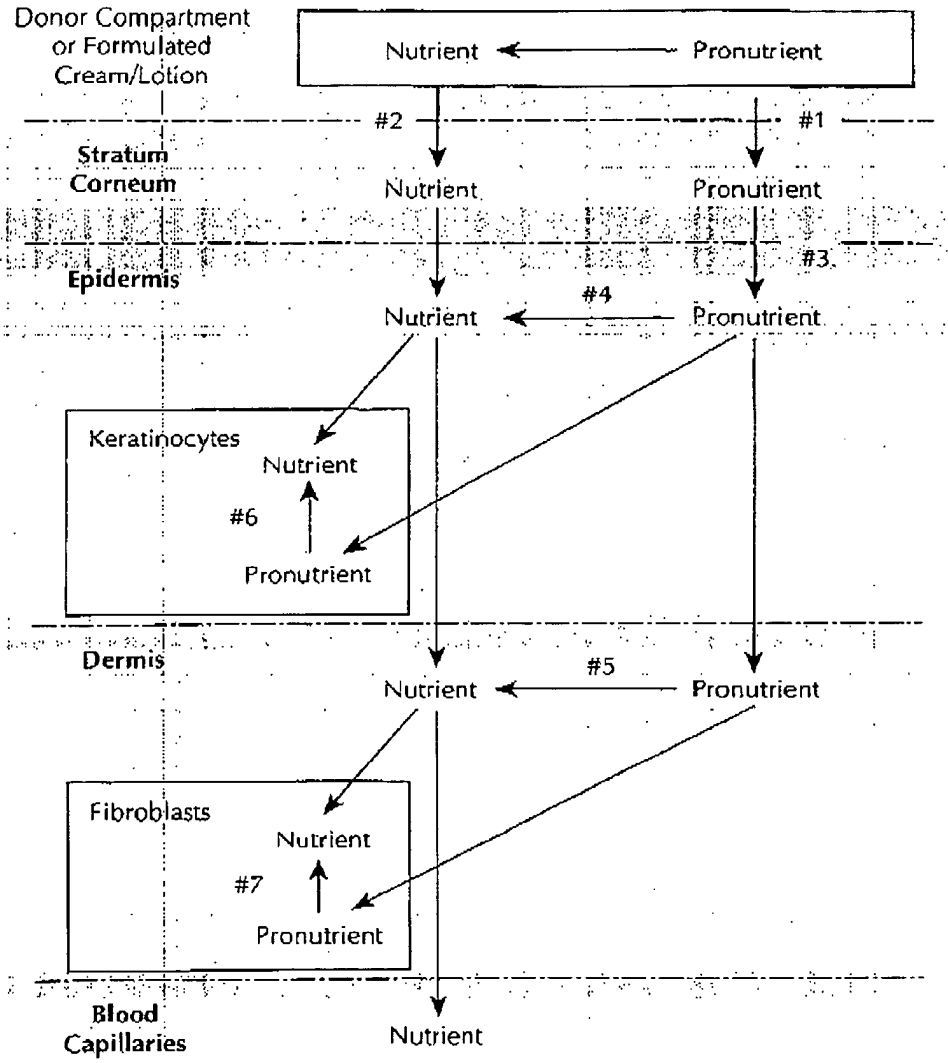

Donor Compartment or Formulated Cream/Lotion
Nutrient
Pronutrient
#2
#1
Stratum Corneum
Nutrient
Pronutrient
Epidermis
#3
#4
Nutrient
Pronutrient
Keratinocytes
Nutrient
#6
Pronutrient
Dermis
#5
Nutrient
Pronutrient
Fibroblasts
Nutrient
#7
Pronutrient
Blood Capillaries
Nutrient

FIG. 2

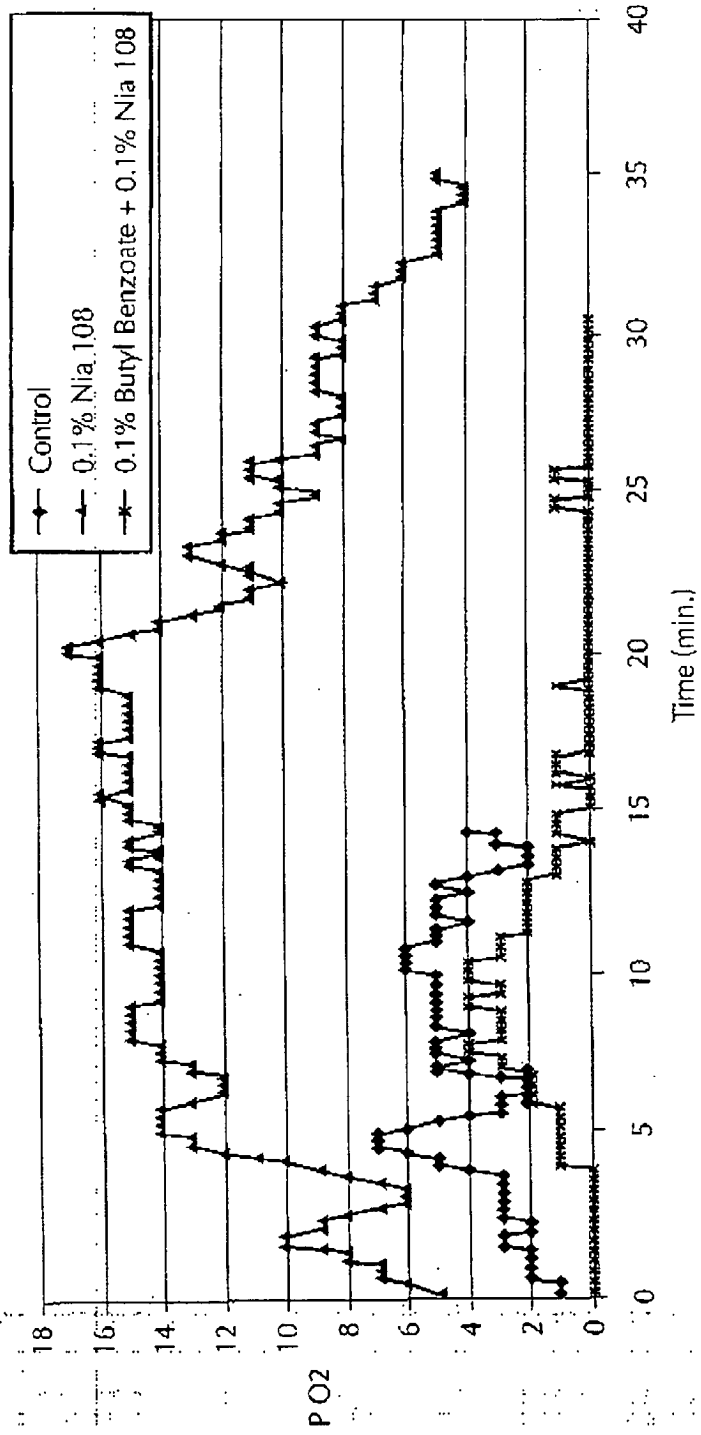

Control
0.1% Nia 108
0.1% Butyl Benzoate + 0.1% Nia 108
PO2
Time (min.)
0
2
4
6
8
10
12
14
16
18
0
5
10
15
20
25
30
35
40

FIG. 3

TOPICAL MICRONUTRIENT DELIVERY SYSTEM AND USES THEREOF

PRIORITY CLAIM

This application claims priority to provisional application No. 60/197,828 filed Apr. 14, 2000, incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to a topical micronutrient delivery system. The system is useful in, e.g., delivery of desirable and/or necessary materials, such as micronutrients, to a subject in need of same. Therapeutic uses of the system are also described.

BACKGROUND AND PRIOR ART

The skin plays multiple roles in protection from environmental insults. Environmental exposure results in the progressive deterioration of skin that is initially cosmetic but can lead to end stage diseases such as actinic keratosis and skin cancer.

Skin deterioration results from damage to DNA and protein, and compelling evidence indicates that reactive oxygen species ("ROS" hereafter) are involved in the generation of DNA damage that results in the loss of genomic integrity of skin cells. Skin cells contain inherent mechanisms for the maintenance of genomic integrity. A growing body of evidence demonstrates that micronutrients including vitamins B6, B12, C, E, folate, and niacin are involved in the maintenance of genomic integrity via mechanisms ranging from scavenging ROS, to the repair of DNA damage. Sub-clinical micronutrient deficiencies are prevalent even in advanced societies and micronutrient status decreases with age.

Skin is a complex organ system, consisting of multiple layers. The uppermost, or "stratum corneum" layer consists of non-living material derived primarily from the terminal differentiation of epidermal keratinocytes, and provides a protective barrier for the underlying components of skin. The epidermis contains a number of cell types, although keratinocytes are the major cell type. Dermal fibroblasts are embedded within a matrix comprised of collagen, elastin, proteoglycans, and other extracellular matrix molecules. Blood capillaries are found in the dermis, but the epidermis is non-vascular.

As people age, progressively deleterious changes in skin appearance occur. The initial changes are the loss of smooth skin texture and the appearance of age spots, followed by changes in elasticity that lead to the appearance of skin wrinkles. The age at which these changes appear and the rate at which one stage progresses to the next varies greatly from individual to individual. During the normal aging process, both the epidermis and dermis become thinner, with a loss of cell number and connective tissue, leading to the appearance of fine wrinkles. Ultraviolet (UV) irradiation from the sun causes photodamage that accelerates skin deterioration. In contrast to the thinning observed in sun-protected skin, photodamaged skin has a thickened and rough appearance with an increase in deeper skin wrinkling. Photodamage also causes end-stage skin deterioration, including pre-malignant lesions termed actinic keratosis, and skin cancer.

Compelling evidence now indicates that oxidative stress, defined as an abnormal accumulation of ROS, is involved in the pathophysiology of skin deterioration. ROS include superoxides, the hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide, peroxynitrite, and hypochlorite. See, e.g., Sivonian, et al., Ann. Rev. Pharmacol. Toxicol. 36:83–106 (1996), incorporated by reference. All cells are

exposed to ROS during the normal course of energy metabolism, via environmental exposure and/or immune surveillance. While ROS are involved in normal cell signaling pathways, elevation of ROS during oxidative stress disrupts signaling pathways, often resulting in cell death by apoptosis or necrosis. Thus, it is likely that ROS are involved in the loss of cell numbers observed even in sun-protected skin over time. Exposure to the ultraviolet rays of sunlight is a major source of skin oxidative stress. Two major targets for damage by ROS in skin are DNA and protein. DNA damage is of particular interest in that unrepaired damage can lead to the loss of skin cells and to an altered function of cells that survive genotoxic stress.

While some changes in skin during aging can not be avoided, much of the skin deterioration that occurs at an early age is avoidable. Skin cells contain a number of protective mechanisms for the prevention and repair of damage to DNA and proteins caused by ROS. First, a number of intracellular molecules, including glutathione and the antioxidant vitamins C and E, play key roles in scavenging ROS before they can react with cellular macromolecules. Indeed, the antioxidant vitamins have already found application in the prevention of skin deterioration, as they are components of many skin creams. Second, cells contain complex mechanisms for the maintenance of genomic integrity. Of particular interest herein is the accumulating evidence for the involvement of micronutrients in maintenance of DNA structure and in DNA repair mechanisms. There are approximately 40 micronutrients that are required, in small amounts, to maintain normal human metabolism (Ames, Ann. N.Y. Acad. Sci 889: 87–106 (1999), incorporated by reference). For many of these micronutrients, a sizeable portion of the population consumes significantly less of the micronutrient than what has been established as the recommended daily intake see Wilson, et al. Data Tables: Combined Results from USDA's 1994 and 1995 continuing survey of food intakes by individuals and 1994 and 1995 diet and health knowledge survey (USDA/ARS Food Surveys Research Group, Beltsville Human Nutrition Research Center, Riverdale, Md. (1997), incorporated by reference. The percentage of the U.S. population that is deficient in a particular micronutrient ranges from 2 to 20%. Ames, supra. To complicate matters, micronutrient status deteriorates further with increasing age. Bates, et al., Br. J. Nutr 82(1):7–15 (1999). Much of our knowledge about the relationship between micronutrients and various diseases such as cancer derives from measurements of micronutrient levels in plasma. While there is much to learn regarding plasma micronutrient levels and target tissue levels, there is evidence that deficiencies observed in plasma are also observed in skin. See Peng, et al., Canc. Epidermiol Biomarkers Prev 2(2): 145–50 (1993). This is not surprising, since the epidermal layer of skin does not contain blood vessels, making delivery of dietary micronutrients to skin inefficient. Of particular concern for skin deterioration are observations that micronutrient deficiencies can mimic radiation- and chemical-induced DNA damage, by effecting single-and double-strand breaks and/or oxidative lesions. Ames, supra. Specifically, deficiencies in folic acid, B12, B6, niacin, vitamin C, vitamin E, iron, and zinc can result in DNA damage. Ames, supra. For each of these micronutrients, there are known metabolic pathways that describe the rationale by which a deficiency results in DNA damage in the absence of genotoxic stress. Additionally, the micronutrient deficiencies would be expected to exacerbate the deleterious effects of genotoxic stress. The above information indicates that improving the micronutrient status of skin cells is desirable, as this will improve the health of skin and likely retard skin deterioration.

It is an object of the invention to provide a topical delivery system which is useful in making micronutrients

available, or making these micronutrients available in greater quantities than possible in the past.

octanol/water partition coefficient ($P_{oct/w}$) are of value in predicting drug transport across skin. A linear correlation